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SANTA BARBARA • SANTA CRUZ

SCHOOL OF MEDICINE
Department of Microbiology
and Immunology

SAN FRANCISCO, CALIFORNIA 94143

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Dr. John S. Cole, III
Program Director, RNA Virus Studies II
Biological Carcinogenesis Branch
Division of Cancer Cause and Prevention
Landow Building, Room 9A22
National Institutes of Health
Bethesda, MD. 20205

Dear John:

I am writing to convey a summary of my impressions from last week's meeting at NIH on hepatitis B virus (HBV) and hepatocellular carcinoma. As a relative newcomer to this field, with my own research still based primarily in retrovirology, I was struck by the extraordinarily slow growth of the number of active investigators in this long-neglected area of virology. In the past, the neglect of hepatitis research was readily understood since the virus could not be studied in cell culture, the agent was highly infectious to personnel, there were no animal models, and the evidence for the involvement of HBV in human cancer was not strong. Now several advances have changed the picture: there are three excellent animal model systems; DNA clones of all the hepatitis B-like genomes are available and can be used to study the organization and expression of viral genes in vitro or in homologous or heterologous cells; and the epidemiological evidence now indicates that HBV may be the most important of all known viruses in the etiology of human cancer. Moreover, the work of Summers and his colleagues on the replication of the duck hepatitis virus (perhaps insufficiently stressed at our meeting) shows that this class of viruses replicates its DNA through RNA intermediates. This is an extraordinary finding, raising countless questions of fundamental importance in eukaryotic biology, and the tools now seem to be at hand for answering them. Work with animal models also seems likely to lead to answers to other basic problems in this area: what is the natural course of hepatitis B virus infection at the molecular level? what are the difficulties of establishing infection in tissue culture with HBV-like viruses? what are the determinants of infection and pathogenicity by HBV-like agents? Similarly, analyses of the human virus genome and of integrated viral DNA in tumors seem likely to answer questions that recurred frequently during our meeting: what are the products and functions of each of the open reading frames in the viral genome? what is the relationship between integrated viral genomes and carcinogenesis? It is also apparent that the development of a successful vaccine (with new and better vaccines probably in the wings), coupled with the abundance of epidemiological information now at hand, will soon permit medically important tests of our ability to control HBV infection and perhaps hepatic cancer. But these clinical matters are beyond my area of competence, and I shall not discuss them further.

The central issue your meeting was intended to address---should the NCI develop special programs to assist advances in hepatitis B research?---is a difficult one given the current climate of fiscal constraint. For reasons stated above, I do believe that the molecular biology of hepatitis B viruses should be studied more widely and with greater financial support than is the case at present. I can envision two basic approaches for achieving this goal.

(1) Provide more funds for those already approved and supported by the usual grant mechanisms. There are currently only about four or five investigators working on experimental models for hepatitis B virus and a slightly larger (and overlapping) contingent studying the molecular aspects of hepatic cancer. It is probable that most of these groups are working with less than the funds requested in their proposals, especially if their grants (like ours) were reviewed recently by study sections responsive to the extreme fiscal crisis that besets basic science at the moment. Administrative readjustment of the budgets recommended by the study sections could be made to allow for the large expenses required for animal maintenance, procural of human specimens from far-off places, protection of personnel, etc., without specific endorsement of new projects.

Another avenue for providing more funds for existing investigators would be to develop a resources program in hepatitis B research, using a board of senior scientists to determine items for funding that would be of general benefit. I can imagine a number of projects that would be suitable: provision of properly prepared tumor and control tissues from African and Asian patients; limited access to chimpanzees for approved studies; centralized pathological examinations of human and animal liver tissues; nucleotide sequencing of the genomes of the two unsequenced animal virus genomes (those of the duck and ground squirrel viruses); preparation of high titre antisera and monoclonal antisera against the major antigens of the four types of hepatitis B virus; synthesis of peptides from open reading frames of the various genomes in prokaryotic expression vectors. The latter items seem sophisticated at first glance, but in fact represent potential bread-and-butter work for the many new recombinant DNA and monoclonal antibody companies that are probably better suited than most university labs for the performance of such tasks. In my view, contract support for narrowly defined projects of this sort would be a more efficient use of funds than the normal grant mechanism.

(2) Attract new investigators to the molecular biology of hepatitis viruses. My experience with the Virus Cancer Program makes me somewhat wary of this approach, since I believe that the investigators most worthy of attention will be drawn to hepatitis research not because of advertised funds but because of inherent intellectual challenges. Many of us have been aware for some time that hepatitis research is generally under-represented at major scientific meetings (e.g. tumor virus meetings) and more often confined to meetings with a strong clinical bias. One avenue for productive use of funds would be to offer support for meetings which specifically include presentation and discussion of recent advances in hepatitis research, or to offer funds for giving a summer course (e.g. at Cold Spring Harbor Laboratories or at NIH) in the molecular biology of hepatitis viruses, open to new and old investigators. Another approach would be to provide special sabbatical post-doctoral, or pre-doctoral support for scholars to work with grant-subsidized investigators in this area.

The most obvious mechanism would be to make requests for new research proposals to be funded by contract or usual granting mechanisms. While I could certainly support such a move, particularly if funds were more freely available than they are now, I also believe that the other suggestions I have made would allow a more efficient use of funds. I would strongly favor any program judged by the usual study sections over a program specially reviewed; in my experience with the contract program through the Virus Cancer Program it seemed difficult to avoid problems of personal bias and excessive funding when such narrowly-defined areas were allocated substantial amounts of money. It would be preferable in my view to enlarge the notion that hepatitis is a "special emphasis area", thereby providing support for applications that fall just below the current funding levels and insuring adequate support for grants that seem harshly trimmed by study sections.

I hope these comments are useful to you.

Sincerely,

Harold E. Varmus, M.D.
Professor

HEV/jm